Complete Summary

GUIDELINE TITLE

Vaccinia (smallpox) vaccine.

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Vaccina (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. MMWR Recomm Rep 2001 Jun 22;50(RR-10):1-25, CE1-7. [89 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Smallpox

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Health Care Providers

Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide guidance for the use of vaccinia (smallpox) vaccine in the United States
- To update the previous Advisory Committee on Immunization Practices recommendations (MMWR 1991;40; No. RR-14:1–10) and include current information regarding the nonemergency use of vaccinia vaccine among laboratory and health-care workers occupationally exposed to vaccinia virus, recombinant vaccinia viruses, and other Orthopoxviruses that can infect humans
- To present recommendations for the use of vaccinia vaccine if smallpox (variola) virus were used as an agent of biological terrorism or if a smallpox outbreak were to occur for another unforeseen reason

TARGET POPULATION

- Laboratory and health-care workers occupationally exposed to vaccinia virus, recombinant vaccinia viruses, and other Orthopoxviruses that can infect humans
- Individuals exposed to smallpox virus as a result of deliberate release by terrorists or for other unforeseen reasons

INTERVENTIONS AND PRACTICES CONSIDERED

1. Routine nonemergency vaccine use [Note: Dryvax®, the vaccinia (smallpox) vaccine currently licensed in the United States, is a lyophilized, live-virus preparation of infectious vaccinia virus (Wyeth Laboratories, Inc., Marietta, Pennsylvania). Vaccinia vaccine does not contain smallpox (variola) virus.]
2. Routine nonemergency revaccination
3. Treatment for vaccine complications; use of vaccinia immunoglobulin (Note: The Centers for Disease Control and Prevention is currently the only source of vaccinia immunoglobulin available to civilians)
4. Preventing contact transmission of vaccinia virus
5. Interpretation of vaccination response
6. Prerelease vaccination in cases of bioterrorist release of smallpox virus
7. Postrelease vaccination in cases of bioterrorist release of smallpox virus
8. Vaccinia immunoglobulin for prophylaxis and treatment of adverse reaction after bioterrorist release or other emergencies

MAJOR OUTCOMES CONSIDERED

Vaccine efficacy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Vaccinia Vaccine

Routine Nonemergency Vaccine Use

Vaccinia vaccine is recommended for laboratory workers who directly handle a) cultures or b) animals contaminated or infected with, nonhighly attenuated vaccinia virus, recombinant vaccinia viruses derived from nonhighly attenuated vaccinia strains, or other Orthopoxviruses that infect humans (e.g., monkeypox, cowpox, vaccinia, and variola). Other health-care workers (e.g., physicians and nurses) whose contact with nonhighly attenuated vaccinia viruses is limited to contaminated materials (e.g., dressings) but who adhere to appropriate infection control measures are at lower risk for inadvertent infection than laboratory workers. However, because a theoretical risk for infection exists, vaccination can be offered to this group. Vaccination is not recommended for persons who do not directly handle nonhighly attenuated virus cultures or materials or who do not work with animals contaminated or infected with these viruses.

Vaccination with vaccinia vaccine results in high seroconversion rates and only infrequent adverse events (see the NGC Guideline Summary field labeled "Potential Harms"). Recipients of standard potency vaccinia vaccine (Dryvax) receive controlled percutaneous doses (approximately 2.5×10^5 PFU) of relatively low pathogenicity vaccinia virus. The resulting immunity should provide protection to recipients against infections resulting from uncontrolled, inadvertent inoculation by unusual routes (e.g., the eye) with a substantial dose of virus of higher or unknown pathogenicity. In addition, persons with preexisting immunity to vaccinia might be protected against seroconversion to the foreign antigen expressed by a recombinant virus if inadvertently exposed. However, persons with preexisting immunity to vaccinia might not receive the full benefit of recombinant vaccinia vaccines developed for immunization against other infections.

Routine Nonemergency Revaccination

According to data regarding the persistence of neutralizing antibody after vaccination, persons working with nonhighly attenuated vaccinia viruses, recombinant viruses developed from nonhighly attenuated vaccinia viruses, or other nonvariola Orthopoxviruses should be revaccinated at least every 10 years. To ensure an increased level of protection against more virulent nonvariola Orthopoxviruses (e.g., monkeypox), empiric revaccination every 3 years can be considered.

Side Effects and Adverse Reactions

See the NGC Guideline Summary field labeled "Potential Harms."

Treatment for Vaccinia Vaccine Complications

Using vaccinia immunoglobulin

The only product currently available for treatment of complications of vaccinia vaccination is vaccinia immunoglobulin, which is an isotonic sterile solution of the immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine. It is effective for treatment of eczema vaccinatum and certain cases of progressive vaccinia; it might be useful also in the treatment of ocular vaccinia resulting from inadvertent implantation. However, vaccinia immunoglobulin is contraindicated for the treatment of vaccinial keratitis. Vaccinia immunoglobulin is recommended for severe generalized vaccinia if the patient is extremely ill or has a serious underlying disease. Vaccinia immunoglobulin provides no benefit in the treatment of postvaccinial encephalitis and has no role in the treatment of smallpox. Current supplies of vaccinia immunoglobulin are limited, and its use should be reserved for treatment of vaccine complications with serious clinical manifestations (e.g., eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and severe ocular viral implantation).

The recommended dosage of the currently available vaccinia immunoglobulin for treatment of complications is 0.6 ml/kg of body weight. Vaccinia immunoglobulin must be administered intramuscularly and should be administered as early as possible after the onset of symptoms. Because therapeutic doses of vaccinia immunoglobulin might be substantial (e.g., 42 ml for a person weighing 70 kg), the product should be administered in divided doses over a 24- to 36-hour period. Doses can be repeated, usually at intervals of 2–3 days, until recovery begins (e.g., no new lesions appear). Future reformulations of vaccinia immunoglobulin might require intravenous administration, and health-care providers should refer to the manufacturer´s package insert for correct dosages and route of administration. Centers for Disease Control and Prevention is currently the only source of vaccinia immunoglobulin for civilians (see the section titled "Vaccinia Vaccine Availability").

Other Treatment Options for Vaccinia Vaccine Complications

The Food and Drug Administration has not approved the use of any antiviral compound for the treatment of vaccinia virus infections or other Orthopoxvirus infections, including smallpox. Certain antiviral compounds have been reported to be active against vaccinia virus or other Orthopoxviruses in vitro and among test animals. However, the safety and effectiveness of these compounds for treating vaccinia vaccination complications or other Orthopoxvirus infections among humans is unknown. Questions also remain regarding the effective dose and the timing and length of administration of these antiviral compounds. Insufficient information exists on which to base recommendations for any antiviral compound to treat postvaccination complications or Orthopoxvirus infections, including smallpox. However, additional information could become available, and health-care providers should consult Centers for Disease Control and Prevention to obtain updated information regarding treatment options for smallpox vaccination complications (see the section titled "Consultation Regarding Complications of Vaccinia Vaccine").

Consultation Regarding Complications of Vaccinia Vaccine

Centers for Disease Control and Prevention can assist physicians in the diagnosis and management of patients with suspected complications of vaccinia vaccination. Vaccinia immunoglobulin is available when indicated. Physicians should telephone

Centers for Disease Control and Prevention at (404) 639-3670 during Mondays–Fridays, except holidays, or (404) 639-3311 during evenings, weekends, and holidays. Health-care workers are requested to report complications of vaccinia vaccination to the Vaccine Adverse Event Reporting System at (800) 822-7967, or to their state or local health department.

Preventing Contact Transmission of Vaccinia Virus

Vaccinia virus can be cultured from the site of primary vaccination beginning at the time of development of a papule (i.e., 2–5 days after vaccination) until the scab separates from the skin lesion (i.e., 14–21 days after vaccination). During that time, care must be taken to prevent spread of the virus to another area of the body or to another person by inadvertent contact. Thorough hand-hygiene with soap and water or disinfecting agents should be performed after direct contact with the site or materials that have come into contact with the site to remove virus from the hands and prevent accidental inoculation to other areas of the body. In addition, care should be taken to prevent contact of the site or contaminated materials from the site by unvaccinated persons. The vaccination site can be left uncovered, or it can be loosely covered with a porous bandage (e.g., gauze) until the scab has separated on its own to provide additional barrier protection against inadvertent inoculation. An occlusive bandage should not be routinely used because maceration of the site might occur. Bandages used to cover the vaccination site should be changed frequently (i.e., every 1–2 days) to prevent maceration of the vaccination site secondary to fluid buildup. Hypoallergenic tape should be used for persons who experience tape hypersensitivity. The vaccination site should be kept dry, although normal bathing can continue. No salves or ointments should be placed on the vaccination site. Contaminated bandages and, if possible, the vaccination site scab, after it has fallen off, should be placed in sealed plastic bags before disposal in the trash to further decrease the potential for inadvertent transmission of the live virus contained in the materials. Clothing or other cloth materials that have had contact with the site can be decontaminated with routine laundering in hot water with bleach.

Recently vaccinated health-care workers should avoid contact with unvaccinated patients, particularly those with immunodeficiencies, until the scab has separated from the skin at the vaccination site. However, if continued contact with unvaccinated patients is unavoidable, health-care workers can continue to have contact with patients, including those with immunodeficiencies, as long as the vaccination site is well-covered and thorough hand-hygiene is maintained. In this setting, a more occlusive dressing might be required. Semipermeable polyurethane dressings (e.g., Opsite®) are effective barriers to vaccinia and recombinant vaccinia viruses. However, exudates can accumulate beneath the dressing, and care must be taken to prevent viral contamination when the dressing is removed. In addition, accumulation of fluid beneath the dressing can increase the maceration of the vaccination site. Accumulation of exudates can be decreased by first covering the vaccination site with dry gauze, then applying the dressing over the gauze. The dressing should also be changed at least once a day. To date, experience with this type of containment dressing has been limited to research protocols. The most critical measure in preventing inadvertent implantation and contact transmission from vaccinia vaccination is thorough hand-

hygiene after changing the bandage or after any other contact with the vaccination site.

Vaccination Method

The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle are the preferred sites for smallpox vaccination. Alcohol or other chemical agents are not required for skin preparation for vaccination unless the area is grossly contaminated. If alcohol is used, the skin must be allowed to dry thoroughly to prevent inactivation of the vaccine by the alcohol. The multiple-puncture technique uses a presterilized bifurcated needle that is inserted vertically into the vaccine vial, causing a droplet of vaccine to adhere between the prongs of the needle. The droplet contains the recommended dosage of vaccine, and its presence within the prongs of the bifurcated needle should be confirmed visually. Holding the bifurcated needle perpendicular to the skin, 15 punctures are rapidly made with strokes vigorous enough to allow a trace of blood to appear after 15–20 seconds. Any remaining vaccine should be wiped off with dry sterile gauze and the gauze disposed of in a biohazard waste container.

Evidence of Immunity and Vaccination-Response Interpretation

Appearance of neutralizing antibodies after vaccination with live vaccinia virus indicates an active immune response that includes the development of antibodies to all viral antigens and increased vaccinia-specific cell-mediated immunity. In a person with normal immune function, neutralizing antibodies appear approximately 10 days after primary vaccination and 7 days after revaccination. Clinically, persons are considered fully protected after a successful response is demonstrated at the site of vaccination. The vaccination site should be inspected 6–8 days after vaccination and the response interpreted at that time. Two types of responses have been defined by the World Health Organization (WHO) Expert Committee on Smallpox. The responses include a) major reaction, which indicates that virus replication has taken place and vaccination was successful; or b) equivocal reaction, which indicates a possible consequence of immunity adequate to suppress viral multiplication or allergic reactions to an inactive vaccine without production of immunity.

Major Reaction

Major (i.e., primary) reaction is defined as a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer. The usual progression of the vaccination site after primary vaccination is as follows:

- The inoculation site becomes reddened and pruritic 3–4 days after vaccination.
- A vesicle surrounded by a red areola then forms, which becomes umbilicated and then pustular by days 7–11 after vaccination.
- The pustule begins to dry; the redness subsides; and the lesion becomes crusted between the second and third week. By the end of approximately the third week, the scab falls off, leaving a permanent scar that at first is pink in color but eventually becomes flesh-colored.

Skin reactions after revaccination might be less pronounced with more rapid progression and healing than those after primary vaccinations. Revaccination is considered successful if a pustular lesion is present or an area of definite induration or congestion surrounding a central lesion (i.e., scab or ulcer) is visible upon examination 6–8 days after revaccination.

Equivocal Reaction

Equivocal reaction, including accelerated, modified, vaccinoid, immediate, early, or immune reactions, are defined as all responses other than major reactions. If an equivocal reaction is observed, vaccination procedures should be checked and the vaccination repeated by using vaccine from another vial or vaccine lot, if available. Difficulty in determining if the reaction was blunted could be caused by immunity, insufficiently potent vaccine, or vaccination technique failure. If the repeat vaccination by using vaccine from another vial or vaccine lot fails to elicit a major reaction, health-care providers should consult Centers for Disease Control and Prevention or their state or local health department before attempting another vaccination.

Misuse of Vaccinia Vaccine

Vaccinia vaccine should not be used therapeutically for any reason. No evidence exists that vaccinia vaccine has any value in treating or preventing recurrent herpes simplex infection, warts, or any disease other than those caused by human Orthopoxviruses. Misuse of vaccinia vaccine to treat herpes infections has been associated with severe complications, including death.

Vaccinia Vaccine Availability

Centers for Disease Control and Prevention is the only source of vaccinia vaccine and vaccinia immunoglobulin for civilians. Centers for Disease Control and Prevention will provide vaccinia vaccine to protect laboratory and other health-care personnel whose occupations place them at risk for exposure to vaccinia and other closely related Orthopoxviruses, including vaccinia recombinants. Vaccine should be administered under the supervision of a physician selected by the institution. Vaccine will be shipped to the responsible physician. Requests for vaccine and vaccinia immunoglobulin, including the reason for the request, should be referred to:

Centers for Disease Control and Prevention
Drug Services, National Center for Infectious Diseases
Mailstop D-09
Atlanta, GA 30333
Telephone: (404) 639-3670
Facsimile: (404) 639-3717
www.cdc.gov

Smallpox Vaccine for Bioterrorism Preparedness

Although use of biological agents is an increasing threat, use of conventional weapons (e.g., explosives) is still considered more likely in terrorism scenarios.

Moreover, use of smallpox virus as a biological weapon might be less likely than other biological agents because of its restricted availability; however, its use would have substantial public health consequences. Therefore, in support of current public health bioterrorism preparedness efforts, the Advisory Committee on Immunization Practices has developed the following recommendations if this unlikely event occurs.

Surveillance

A suspected case of smallpox is a public health emergency. Smallpox surveillance in the United States includes detecting a suspected case or cases, making a definitive diagnosis with rapid laboratory confirmation at CDC, and preventing further smallpox transmission. A suspected smallpox case should be reported immediately by telephone to state or local health officials and advice obtained regarding isolation and laboratory specimen collection. State or local health officials should notify CDC immediately if a suspected case of smallpox is reported. Because of the problems encountered previously in Europe with health-care–associated smallpox transmission from imported cases present in a hospital setting, health officials should be diligent regarding use of adequate isolation facilities and precautions (see the section titled "Infection Control Measures"). Currently, specific therapies with proven treatment effectiveness for clinical smallpox are unavailable. Medical care of more seriously ill smallpox patients would include supportive measures only. If the patient´s condition allows, medical and public health authorities should consider isolation and observation outside a hospital setting to prevent health-care–associated smallpox transmission and overtaxing of medical resources. Clinical consultation and a preliminary laboratory diagnosis can be completed within 8–24 hours. Surveillance activities, including notification procedures and laboratory confirmation of cases, might change if smallpox is confirmed.

Prerelease Vaccination

The risk for smallpox occurring as a result of a deliberate release by terrorists is considered low, and the population at risk for such an exposure cannot be determined. Therefore, preexposure vaccination is not recommended for any group other than laboratory or medical personnel working with nonhighly attenuated Orthopoxviruses (see the section titled "Routine Nonemergency Vaccine Use").

Recommendations regarding preexposure vaccination should be on the basis of a calculable risk assessment that considers the risk for disease and the benefits and risks regarding vaccination. Because the current risk for exposure is considered low, benefits of vaccination do not outweigh the risk regarding vaccine complications. If the potential for an intentional release of smallpox virus increases later, preexposure vaccination might become indicated for selected groups (e.g., medical and public health personnel or laboratorians) who would have an identified higher risk for exposure because of work-related contact with smallpox patients or infectious materials.

Postrelease Vaccination

If an intentional release of smallpox (variola) virus does occur, vaccinia vaccine will be recommended for certain groups. Groups for whom vaccination would be indicated include:

- persons who were exposed to the initial release of the virus
- persons who had face-to-face, household, or close-proximity contact (<6.5 feet or 2 meters) with a confirmed or suspected smallpox patient at any time from the onset of the patient´s fever until all scabs have separated
- personnel involved in the direct medical or public health evaluation, care, or transportation of confirmed or suspected smallpox patients
- laboratory personnel involved in the collection or processing of clinical specimens from confirmed or suspected smallpox patients
- other persons who have an increased likelihood of contact with infectious materials from a smallpox patient (e.g., personnel responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present)

Using recently vaccinated personnel (i.e., <3 years) for patient care activities would be the best practice. However, because recommendations for routine smallpox vaccination in the United States were rescinded in 1971 and smallpox vaccination is currently recommended only for specific groups (see the section titled "Routine Nonemergency Vaccine Use"), having recently vaccinated personnel available in the early stages of a smallpox emergency would be unlikely. Smallpox vaccine can prevent or decrease the severity of clinical disease, even when administered 3–4 days after exposure to the smallpox virus. Preferably, healthy persons with no contraindications to vaccination, who can be vaccinated immediately before patient contact or very soon after patient contact (i.e., $\leq$3 days), should be selected for patient care activities or activities involving potentially infectious materials. Persons who have received a previous vaccination (i.e., childhood vaccination or vaccination >3 years before) against smallpox might demonstrate a more accelerated immune response after revaccination than those receiving a primary vaccination. If possible, these persons should be revaccinated and assigned to patient care activities in the early stages of a smallpox outbreak until additional personnel can be successfully vaccinated.

Personnel involved with direct smallpox patient care activities should observe strict contact and airborne precautions (i.e., gowns, gloves, eye shields, and correctly fitted N-95 masks) for additional protection until postvaccination immunity has been demonstrated (i.e., 6–8 days after vaccination). Shoe covers should be used in addition to standard contact isolation protective clothing to prevent transportation of the virus outside the isolation area. After postvaccination immunity has occurred, contact precautions with shoe covers should still be observed to prevent the spread of infectious agents (see the section titled "Infection Control Measures"). If possible, the number of personnel selected for direct contact with confirmed or suspected smallpox patients or infectious materials should be limited to reduce the number of vaccinations and to prevent unnecessary vaccination complications.

Children who have had a definite risk regarding exposure to smallpox (i.e., face-to-face, household, or close-proximity contact with a smallpox patient) should be vaccinated regardless of age. Pregnant women who have had a definite exposure to smallpox virus (i.e., face-to-face, household, or close-proximity contact with a

smallpox patient) and are, therefore, at high risk for contracting the disease, should also be vaccinated. Smallpox infection among pregnant women has been reported to result in a more severe infection than among nonpregnant women. Therefore, the risks to the mother and fetus from experiencing clinical smallpox substantially outweigh any potential risks regarding vaccination. In addition, vaccinia virus has not been documented to be teratogenic, and the incidence of fetal vaccinia is low. When the level of exposure risk is undetermined, the decision to vaccinate should be made after assessment by the clinician and patient of the potential risks versus the benefits of smallpox vaccination.

In a postrelease setting, vaccination might be initiated also for other groups whose unhindered function is deemed essential to the support of response activities (e.g., selected law enforcement, emergency response, or military personnel) and who are not otherwise engaged in patient care activities but who have a reasonable probability of contact with smallpox patients or infectious materials. If vaccination of these groups is initiated by public health authorities, only personnel with no contraindications to vaccination should be vaccinated before initiating activities that could lead to contact with suspected smallpox patients or infectious materials. Steps should be taken (e.g., reassignment of duties) to prevent contact of any unvaccinated personnel with infectious smallpox patients or materials.

Because of increased transmission rates that have been described in previous outbreaks of smallpox involving aerosol transmission in hospital settings, potential vaccination of nondirect hospital contacts should be evaluated by public health officials. Because hospitalized patients might have other contraindications to vaccination (e.g., immunosuppression), vaccination of these nondirect hospital contacts should occur after prudent evaluation of the hospital setting with determination of the exposure potential through the less-common aerosol transmission route.

Contraindications to Vaccination During a Smallpox Emergency

See the NGC Guideline Summary field labeled "Subgroups Most Likely to Experience Harms."

Infection Control Measures

Isolation of confirmed or suspected smallpox patients will be necessary to limit the potential exposure of nonvaccinated and, therefore, nonimmune persons. Although droplet spread is the major mode of person-to-person smallpox transmission, airborne transmission through fine-particle aerosol can occur. Therefore, airborne precautions using correct ventilation (e.g., negative air-pressure rooms with high-efficiency particulate air filtration) should be initiated for hospitalized confirmed or suspected smallpox patients, unless the entire facility has been restricted to smallpox patients and recently vaccinated persons. Although personnel who have been vaccinated recently and who have a demonstrated immune response should be fully protected against infection with variola virus (see the section titled "Evidence of Immunity and Vaccination-Response Interpretation"), they should continue to observe standard and contact precautions (i.e., using protective clothing and shoe covers) when in contact with smallpox patients or contaminated materials to prevent inadvertent spread of

variola virus to susceptible persons and potential self-contact with other infectious agents. Personnel should remove and correctly dispose of all protective clothing before contact with nonvaccinated persons. Reusable bedding and clothing can be autoclaved or laundered in hot water with bleach to inactivate the virus. Laundry handlers should be vaccinated before handling contaminated materials.

Nonhospital isolation of confirmed or suspected smallpox patients should be of a sufficient degree to prevent the spread of disease to nonimmune persons during the time the patient is considered potentially infectious (i.e., from the onset of symptoms until all scabs have separated). Private residences or other nonhospital facilities that are used to isolate confirmed or suspected smallpox patients should have nonshared ventilation, heating, and air-conditioning systems. Access to those facilities should be limited to recently vaccinated persons with a demonstrated immune response. If suspected smallpox patients are placed in the same isolation facility, they should be vaccinated to guard against accidental exposure caused by misclassification as someone with smallpox.

In addition to isolation of infectious smallpox patients, careful surveillance of contacts during their potential incubation period is required. Transmission of smallpox virus rarely occurs before the appearance of the rash that develops 2–4 days after the prodromal fever. If a vaccinated or unvaccinated contact experiences a fever >101 degrees F (38 degrees C) during the 17-day period after his or her last exposure to a smallpox patient, the contact should be isolated immediately to prevent contact with nonvaccinated or nonimmune persons until smallpox can be ruled out by clinical or laboratory examination.

Vaccinia Immunoglobulin for Prophylaxis and Treatment of Adverse Reactions During a Smallpox Emergency

If vaccination of persons with contraindications is required because of exposure to smallpox virus after an intentional release as a bioterrorism agent, current stores of vaccinia immunoglobulin are insufficient to allow its prophylactic use with vaccination. Because of the limited stores of vaccinia immunoglobulin, its use in such a scenario should be reserved for severe, life-threatening complications (e.g., progressive vaccinia, eczema vaccinatum, or severe, toxic generalized vaccinia). If additional vaccinia immunoglobulin becomes available in sufficient quantities to allow its prophylactic use, vaccinia immunoglobulin should be administered intramuscularly as a dose of 0.3 mg/kg along with vaccinia vaccine to persons with contraindications who require vaccination.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Throughout the guideline document, the evidence used as the basis for specific recommendations is discussed briefly.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Neutralizing antibodies induced by vaccinia vaccine are genus-specific and cross-protective for other Orthopoxviruses (e.g., monkeypox, cowpox, and variola viruses). Although the efficacy of vaccinia vaccine has never been measured precisely during controlled trials, epidemiologic studies demonstrate that an increased level of protection against smallpox persists for <5 years after primary vaccination and substantial but waning immunity can persist for >10 years. Antibody levels after revaccination can remain high longer, conferring a greater period of immunity than occurs after primary vaccination alone. Administration of vaccinia vaccine within the first days after initial exposure to smallpox virus can reduce symptoms or prevent smallpox disease.

Although the level of antibody that protects against smallpox infection is unknown, after percutaneous administration of a standard dose of vaccinia vaccine, >95% of primary vaccinees (i.e., persons receiving their first dose of vaccine) will experience neutralizing or hemagglutination inhibition antibody at a titer of >1:10. Neutralizing antibody titers of >1:10 persist among 75% of persons for 10 years after receiving second doses and <30 years after receiving three doses of vaccine. The level of antibody required for protection against vaccinia virus infection is unknown also. However, when lack of local skin response to revaccination with an appropriately administered and potent vaccine dose is used as an indication of immunity, <10% of persons with neutralizing titers of >1:10 exhibit a primary-type response at revaccination, compared with >30% of persons with titers <1:10. Lack of major or primary-type reaction can indicate the presence of neutralizing antibody levels sufficient to prevent viral replication, although it can also indicate unsuccessful vaccination because of improper administration or less potent vaccine.

POTENTIAL HARMS

Vaccine Recipients

Side Effects and Less Severe Adverse Reactions

In a nonimmune person who is not immunosuppressed, the expected response to primary vaccination is the development of a papule at the site of vaccination 2–5 days after percutaneous administration of vaccinia vaccine. The papule becomes vesicular, then pustular, and reaches its maximum size in 8–10 days. The pustule dries and forms a scab, which separates within 14–21 days after vaccination, leaving a scar. Primary vaccination can produce swelling and tenderness of regional lymph nodes, beginning 3–10 days after vaccination and persisting for 2–4 weeks after the skin lesion has healed. Maximum viral shedding from the vaccination site occurs 4–14 days after vaccination, but vaccinia can be recovered from the site until the scab separates from the skin.

A fever is also common after the vaccine is administered. Approximately 70% of children experience ≥1 day of temperatures ≥100 degrees F for 4–14 days after primary vaccination, and 15%–20% of children experience temperatures ≥102 degrees F. After revaccination, 35% of children experience temperatures ≥100 degrees F, and 5% experience temperatures of ≥102 degrees F. Fever is less common among adults after vaccination or revaccination.

Inadvertent inoculation at other sites is the most frequent complication of vaccinia vaccination and accounts for approximately half of all complications of primary vaccination and revaccination. Inadvertent inoculation usually results from autoinoculation of vaccinia virus transferred from the site of vaccination. The most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum. Most lesions heal without specific therapy, but vaccinia immunoglobulin can be useful for cases of ocular implantation (see the section titled "Treatment for Vaccinia Vaccine Complications"). However, if vaccinial keratitis is present, vaccinia immunoglobulin is contraindicated because it might increase corneal scarring.

Erythematous or urticarial rashes can occur approximately 10 days after primary vaccination and can be confused with generalized vaccinia. However, the vaccinee is usually afebrile with this reaction, and the rash resolves spontaneously within 2–4 days. Rarely, bullous erythema multiforme (i.e., Stevens-Johnson syndrome) occurs.

Moderate to Severe Adverse Reactions

Moderate and severe complications of vaccinia vaccination include eczema vaccinatum, generalized vaccinia, progressive vaccinia, and postvaccinial encephalitis. These complications are rare but occur ≥10 times more often among primary vaccinees than among revaccinees and are more frequent among infants than among older children and adults. A study of Israeli military recruits aged ≥ 18 years, who were vaccinated during 1991–1996, reported rates of the severe complications progressive vaccinia (i.e., vaccinia necrosum rate: 0/10,000 vaccinees) and postvaccinial encephalitis (rate: 0/10,000 vaccinees) similar to those reported in previous studies.

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus among persons who have eczema or a history of eczema or other chronic or exfoliative skin conditions (e.g., atopic dermatitis). Usually, illness is mild and self-limited but can be severe or fatal. The most serious cases among vaccine recipients occur among primary vaccinees and are independent of the activity of the underlying eczema. Severe cases have been observed also after contact of recently vaccinated persons with persons who have active eczema or a history of eczema (see the section titled "Contacts of Vaccinees").

Generalized vaccinia is characterized by a vesicular rash of varying extent that can occur among persons without underlying illnesses. The rash is generally self-limited and requires minor or no therapy except among patients whose conditions might be toxic or who have serious underlying immunosuppressive illnesses (e.g., acquired immunodeficiency syndrome [AIDS]).

Progressive vaccinia (vaccinia necrosum) is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. It has occurred almost exclusively among persons with cellular immunodeficiency. The most serious complication is postvaccinial encephalitis. In the majority of cases, it affects primary vaccinees aged <1 year or adolescents and adults receiving a primary vaccination. Occurrence of this complication was influenced by the strain of vaccine virus and was higher in Europe than in the United States. The principle strain of vaccinia virus used in the United States, NYCBOH, was associated with the lowest incidence of postvaccinial encephalitis. Approximately 15%–25% of affected vaccinees with this complication die, and 25% have permanent neurological sequelae. Fatal complications caused by vaccinia vaccination are rare, with approximately 1 death/million primary vaccinations and 0.25 deaths/million revaccinations. Death is most often the result of postvaccinial encephalitis or progressive vaccinia.

Contacts of Vaccinees

Transmission of vaccinia virus can occur when a recently vaccinated person has contact with a susceptible person. In a 1968 10-state survey of complications of vaccinia vaccination, the risk for transmission to contacts was 27 infections/million total vaccinations; 44% of those contact cases occurred among children aged ≤5 years. Before the U.S. military discontinued routine smallpox vaccination in 1990, occurrences of contact transmission of vaccinia virus from recently vaccinated military recruits had been reported, including six cases resulting from transmission from one vaccine recipient. Approximately 60% of contact transmissions reported in the 1968 10-state survey resulted in inadvertent inoculation of otherwise healthy persons. Approximately 30% of the eczema vaccinatum cases reported in that study were a result of contact transmission. Eczema vaccinatum might be more severe among contacts than among vaccinated persons, possibly because of simultaneous multiple inoculations at several sites. Contact transmission rarely results in postvaccinial encephalitis or vaccinia necrosum.

CONTRAINDICATIONS

CONTRAINDICATIONS

Routine Nonemergency Laboratory and Health-Care Worker Contraindications

The following contraindications to vaccination apply to routine nonemergency use of vaccinia vaccine (see the section titled "Contraindications to Vaccination During a Smallpox Emergency"). Before administering vaccinia vaccine, the physician should complete a thorough patient history to document the absence of vaccination contraindications among both vaccinees and their household contacts. Efforts should be made to identify vaccinees and their household contacts who have eczema, a history of eczema, or immunodeficiencies. Vaccinia vaccine should not be administered for routine nonemergency indications if these conditions are present among either recipients or their household contacts.

History or Presence of Eczema or Other Skin Conditions

Because of the increased risk for eczema vaccinatum, vaccinia vaccine should not be administered to persons with eczema of any degree, those with a past history of eczema, those whose household contacts have active eczema, or whose household contacts have a history of eczema. Persons with other acute, chronic, or exfoliative skin conditions (e.g., atopic dermatitis, burns, impetigo, or varicella zoster) might also be at higher risk for eczema vaccinatum and should not be vaccinated until the condition resolves.

Pregnancy

Live-viral vaccines are contraindicated during pregnancy; therefore, vaccinia vaccine should not be administered to pregnant women for routine nonemergency indications. However, vaccinia vaccine is not known to cause congenital malformations. Although <50 cases of fetal vaccinia infection have been reported, vaccinia virus has been reported to cause fetal infection on rare occasions, almost always after primary vaccination of the mother. Cases have been reported as recently as 1978. When fetal vaccinia does occur, it usually results in stillbirth or death of the infant soon after delivery.

Altered Immunocompetence

Replication of vaccinia virus can be enhanced among persons with immunodeficiency diseases and among those with immunosuppression (e.g., as occurs with leukemia, lymphoma, generalized malignancy, solid organ transplantation, cellular or humoral immunity disorders, or therapy with alkylating agents, antimetabolites, radiation, or high-dose corticosteroid therapy [i.e., $\geq$2 mg/kg body weight or 20 mg/day of prednisone for $\geq$2 weeks]). Persons with immunosuppression also include hematopoietic stem cell transplant recipients who are <24 months posttransplant, and hematopoietic stem cell transplant recipients who are $\geq$24 months posttransplant but who have graft-versus-host disease or disease relapse. Persons with such conditions or whose household contacts have such conditions should not be administered vaccinia vaccine.

Persons Infected with Human Immunodeficiency Virus (HIV)

Risk for severe complications after vaccinia vaccination for persons infected with HIV is unknown. One case of severe generalized vaccinia has been reported involving an asymptomatic HIV-infected military recruit after the administration of multiple vaccines that included vaccinia vaccine. Additionally, a 1991 report indicated that two HIV-infected persons might have died of a progressive vaccinia-like illness after treatment with inactivated autologous lymphocytes infected with a recombinant HIV-vaccinia virus. No evidence exists that smallpox vaccination accelerates the progression of HIV-related disease. However, the degree of immunosuppression that would place an HIV-infected person at greater risk for adverse events is unknown. Because of this uncertainty, until additional information becomes available, not vaccinating persons (under routine nonemergency conditions) who have HIV infection is advisable.

Infants and Children

Before the eradication of smallpox, vaccinia vaccination was administered routinely during childhood. However, smallpox vaccination is no longer indicated for infants or children for routine nonemergency indications.

Persons with Allergies to Vaccine Components

The currently available vaccinia vaccine (i.e., Dryvax) contains trace amounts of polymyxin B sulfate, streptomycin sulfate, chlortetracycline hydrochloride, and neomycin sulfate. Persons who experience anaphylactic reactions (i.e., hives, swelling of the mouth and throat, difficulty breathing, hypotension, and shock) to any of these antibiotics should not be vaccinated. Vaccinia vaccine does not contain penicillin. Future supplies of vaccinia vaccine will be reformulated and might contain other preservatives or stabilizers. Refer to the manufacturer´s package insert for additional information.

Contraindications to Vaccination During a Smallpox Emergency

No absolute contraindications exist regarding vaccination of a person with a high-risk exposure to smallpox. Persons at greatest risk for experiencing serious vaccination complications are also at greatest risk for death from smallpox. If a relative contraindication to vaccination exists, the risk for experiencing serious vaccination complications must be weighed against the risk for experiencing a potentially fatal smallpox infection. When the level of exposure risk is undetermined, the decision to vaccinate should be made after prudent assessment by the clinician and the patient of the potential risks versus the benefits of smallpox vaccination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Vaccina (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. MMWR Recomm Rep 2001 Jun 22;50(RR-10):1-25, CE1-7. [89 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Jun

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Advisory Committee on Immunization Practices

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Names of Committee Members: John F. Modlin, M.D. (Chairman); Dixie E. Snider, Jr., M.D., M.P.H. (Executive Secretary); Dennis A. Brooks, M.D., M.P.H.; Richard D. Clover, M.D.; Jaime Deseda-Tous, M.D.; Charles M. Helms, M.D., Ph.D.; David R. Johnson, M.D., M.P.H.; Myron J. Levin, M.D.; Paul A. Offit, M.D.; Margaret B. Rennels, M.D.; Natalie J. Smith, M.D., M.P.H.; Lucy S. Tompkins, M.D., Ph.D.; Bonnie M. Word, M.D.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline. It updates the previous Advisory Committee on Immunization Practices (ACIP) recommendations (MMWR 1991;40; No. RR-14:1-10).

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site in HTML format.

The document is also available in Portable Document Format (PDF).

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

Additional information regarding Smallpox preparation and response activities is available from the Centers for Disease Control and Prevention (CDC) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 27, 2001.

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